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10/802,220	03/17/2004	Masaki Sunami	227833	3562

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EXAMINER	
PAGONAKIS, ANNA	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/802,220	SUNAMI ET AL.	
	Examiner	Art Unit	
	Anna Pagonakis	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9; 11-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

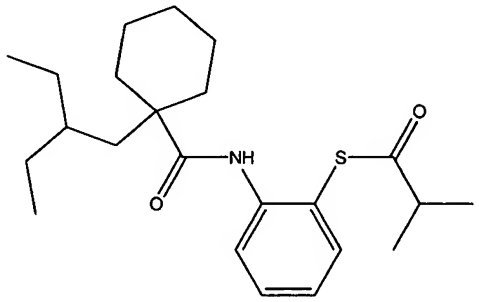
Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of cholesteryl ester transfer protein inhibitor wherein R is a substituted C_{3-10} cycloalkyl group; X_1, X_2, X_3, and X_4 are each hydrogen; and Z is $-YR_1$, wherein Y is –CO and R_1 is an unsubstituted branched C_{1-10} alkyl group in the reply filed on August 19, 2007 is acknowledged. The elected species is a compound with the structure:



Claims 1-9, 11-23 read on the elected cholesteryl ester transfer protein inhibitor.

Applicant's election with traverse of the cardiovascular disease hyperlipidemia in the reply on August 19, 2007 is acknowledged. Claims 15-23 read on the elected species.

The traversal of both species is on the ground that maintaining the specie election requirement will not lead to an undue search burden. This is not found persuasive because various species are separate and distinct and can thus acquire their own patent. Therefore, the restriction is hereby made FINAL.

Claim 10 is withdrawn from consideration as being drawn to non-elected subject matter.

Information Disclosure Statement

Applicant's Information Disclosure Statements filed on April 1, 2004; October 12, 2004; October 26, 2004 and December 13, 2004 have been acknowledged. Documents not in English or not provided were not considered in the examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 3, and 4 recites the limitation "cholesteryl ester transfer protein," the claim depends on claim 1. There is insufficient antecedent basis for this limitation in claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The limitation, "a major portion," is indefinite because it is not clear to what extent the cholesteryl ester transfer protein must be crystalline.

Claims 3, 5, 7-9, 11 and 13-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. The limitation, "substantially" found in claim 3 is indefinite because it is not clear to what extent the cholesteryl ester transfer protein must be crystalline.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a cardiovascular disorder in a mammal, does not reasonably provide enablement for "prophylaxis" of a cardiovascular disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is a scope of enablement rejection.

In the instant case, the claims recite a method for "the treatment or prophylaxis of a cardiovascular disorder in a mammal" comprising administering the elected compound. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the applications coupled with information known in the art without undue experimentation (*United States v. Teletronics* Inc., 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2nd 1400 (Fed. Cir. 1988).

These factors include the following:

1. Amount of guidance provided by the Applicant.

While the applicant has demonstrated within the application that the elected compound is effective as a possible treatment for cardiovascular disorders, the generic Claim 5 and 9 is massive, and only the elected compound is tested. No reference is made as to how to "prevent" a cardiovascular disorder.

2. Unpredictability of the art

It is well established that "scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. (USPQ 18, 24 (CCPA 1970). See *In re Fisher*, 427 F.2d 833, 839, 166.

The term "prophylaxis" in the present claims is considered to be comparable to the word "prevent," and both circumscribe methods of absolute success. That is, in order to be enabled to practice the present invention, the skilled artisan would have to accept that by administering the presently claimed active agent(s), the incidence of cardiovascular disorder would be 0% and there would be a reasonable guarantee that a cardiovascular disorder would never develop. Such a situation is sufficiently unusual that data would need to be shown in order to establish that cardiovascular disorders could be kept from ever occurring through the administration of the claimed active agent. Because absolute success is not reasonably possible with most diseases or disorders, especially a condition as complex and poorly understood as cardiovascular disorders, the specification, which lacks an objective showing that such a disease could be prevented, is viewed as lacking an enabling disclosure of the same. Applicant must show that the Claimed

method "prevents" a cardiovascular disorder in all instances in all situations. The specification fails to fully enable the claimed compound for the prevention of a cardiovascular disorder. Cardiovascular disorders can often be prevented through good diet and exercise. However, many people cannot prevent cardiovascular disease because they are born with a genetic predisposition (http://heartcenter.uc.edu/global.cfm?SecId=Cardiology).

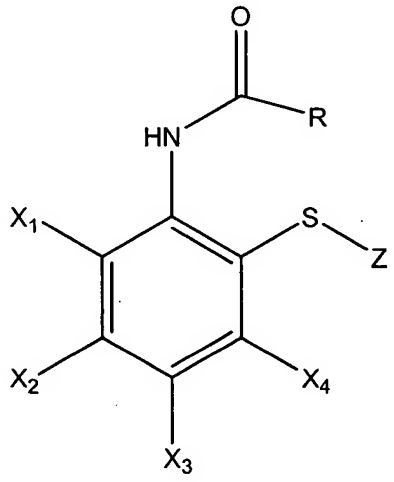
The specification dose not teach any working examples nor provide substantive evidence that the claimed compound is capable of inducing protective immunity against a cardiovascular disorder. In fact, the instant specification demonstrates that the administration of the elected compound is capable of aiding in the treatment of hyperlipidemia, but would this necessarily imply the prevention of any cardiovascular disorder? This demonstration of prevention is required for the skilled artisan to be able to use the claimed compound for their intended purpose of preventing a cardiovascular disorder. Without this demonstration, the skilled artisan would not be able to reasonably predict if the cardiovascular disorder has been completely disabled or eliminated.

3. Number of working examples

Applicant has provided numbers example compounds however has only tested the elected compound of the large number of compounds that exist in the broad Claims 5 and 9.

4. Scope of the claims

The scope of the claims involve all of the thousands of compounds of general formula (I):



Thus, the scope of the claims is very broad.

5. Nature of the invention

The invention relates to a pharmaceutical composition comprising a cholesteryl ester transfer protein inhibitor and crospovidone and using said composition a method for the treatment or prophylaxis of a cardiovascular disorder.

6. Level of skill in the art

The artisan using Applicants invention would be a physician with an M.D. degree, and having several years of experience.

MPEP 2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time of the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2nd 1510m 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here that Applicant is

not enabled for making most of the compounds or compositions mentioned in the current application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 5-9; 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gumkowski *et al* (US PGPub 20060014788) in view of Ault *et al* (US Patent 7,049,283).

Gumkowski *et al.* teaches pharmaceutical compositions comprising a CETP inhibitor, including the claimed compound, i.e., "Compound B", (see page 48, col. 1), as well as various co-solvents, surfactants and, optionally a digestible oil, (page 5, cols. 1-2, paragraphs [0048]-[0098]). The composition may be presented in various forms, such as solutions, suspensions, emulsions or as fill in encapsulated dosage forms such as hard or soft gelatin capsules (page 2, paragraph [0018]). The amount of compound which may be the composition is taught to range from 5 to about 500, (page 6, middle of paragraph [0012]). Gunkowski et al. further teach that the compositions, e.g., the pre-concentrates used to fill the capsules, may be added to sodas or foods such as ice cream (page 6, col. 2, last sentence of paragraph [0012]).

Gumkowski et al. further teach that the administration of such above compositions can be useful for the raising of HDL cholesterol, lowering LDL cholesterol and treating atherosclerosis, i.e., they teach that one of the problems they solved was "for a well-tolerated agent that can significantly elevate plasma HDL levels, thereby reversing or slowing the progression of atherosclerosis" (sentence bridging cols. 1-2 on page 1). Further, it is taught that their invention "relates to encapsulated formulations of [CETP] inhibitors, see for use in mammals, especially humans, which for mutations provide increased concentrations of CETP inhibitors for absorption, hence higher bioavailability", (page 1, paragraph [0001], emphasis added).

Ault *et al.* teaches a composition suitable for oral delivery of pharmacologically active agents, comprising a therapeutically-effective amount of a pharmacologically active agent; a crospovidone or povidone; and a delivery agent for said pharmacologically active agent are disclosed. The compositions provide excellent oral bioavailability of pharmacologically active agents (abstract). Furthermore, the reference teaches that the composition containing crospovidone versus the comparative compositions which do not contain crospovidone, resulting in greatly enhanced oral bioavailability of the formulations according to the instant invention (column 9, lines 34-38).

One of ordinary skill in the art would have been motivated to combine the above references and as combined would teach the inventions as claimed. One of ordinary skill in the art would have been motivated to combine the teachings of Gumkowski et al. and Ault et al., since Gumkowski et al. teaches that the claimed compound results in increased bioavailability with encapsulation. Furthermore, Ault et al. teaches that crospovidone results in more bioavailable

formulations. It would be obvious skilled to one in the art to combine a substance that results in increased bioavailability (crospovidone) to another substance in need of becoming more bioavailable (elected compound).

Claim 5-9; 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shinkai *et al* (US Patent 6,426,365) in view of Sanbar et al. (Circulation, Volume XXXVIII. October 1968).

Shinkai et al. teach pharmaceutical compositions comprising a CETP inhibitor, including the claimed compound, i.e., at Example 26, (see cols. 61-62), as well as various known pharmacologically acceptable carriers, sweetners and flavor improving agents, which may be presented for oral or parenteral administration, including the form of tablets (col. 30, lines 28-47, especiallylines 34, 36, 40 and 47). Respecting the biological activity of the compound, Shinkai et al. teach CETP inhibitory activity at, for example, the abstract at line 1 and col. 120, line 65-66 and Tables 38-48. Further, the patentees teach that the compound is effective for the treatment of atherosclerosis or hyperlipidemia because of the compound to increase HDL and also decreasing levels of LDL (col. 4, lines 21-27).

Sanbar et al. teaches that polyvinylpyrrolidone is capable of a hypolipidemic effect. In particular, "in hyperlipidemic human subjects, intravenous administration of PVP substantially diminishes serum cholesterol and triglyceride concentrations, which is in keeping with the data by others in normal and hyperlipidemic nephrotic rats (page 774, under Discussion). According to "Polyvinylpyrrolidone Excipients for Pharmaceuticals: Povidone, Crospovidone and

Copovidone," polyvinylpolypyyrrolidone is another commonly used name for crospovidone (page 126, table 114).

One of ordinary skill in the art would have been motivated to combine the above references and as combined would teach the invention as claimed. One of ordinary skill in the art would have been motivated to combine Shinkai et al. and Sanbar et al. because both are ditected to the treatment of hyperlipidemia. Moreover, combining agents which are known to be useful anti-cancer agents individually into a single compositions useful for the very same purpose is prima facie obvious. See In Re Kerkhoven 205 USPQ 1069. Since it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose, the idea of combining the elected compound and crospovidone flows logically from having been individually taught in the prior art.

Claim 6 is drawn to the elected compound and crospovidone in crystalline form. This would also have been obvious. Englert et al. teaches a crystalline form of a benzamide and processes for their preparation, their use, and pharmaceutical preparations comprising them (abstract). Given the benzamide structure of the claimed compound it would have been obvious to utilize the crystallization techniques outlined in Englert et al. to achieve a crystalline product/formulation.

Also, the "about" limitation in claims 7 and 13 encompasses thereby any amount provided that the remainder of the claim embodiment limitations are anticipated by the prior art reference.

Regarding claims 18-23, it is the Examiner's position that the instantly claimed method is inherently taught by the reference. It is noted that *In re Best* (195 USPQ 430) and *In re Ftizgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not posses the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1669 (Fed. Cir. 2004). ("[T]he fact that a characteristic is a necessary feature or result of a prior art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipate, even if that fact was unknown at the time of the prior invention"). The concentration of the cholesteryl ester transfer protein inhibitor present in the bloodstream are inherently determined by the particular drug/medication.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re*

Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-9; 11-23 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-24 of U.S Patent No. 6,426,365 (Shinkai et al.), U.S. Patent No. 6,753,346 (Shinkai et al.) or provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent Application No. 10/825, 531.

Although the conflicting claims are not identical, they are not patentably distinct from each other because in practicing the instantly claimed methods of increasing bioavailability; increasing the extent of absorption or treating a cardiovascular disease such as hyperlipidemia, one would necessarily have to be practicing the claimed subject matter of '365 or '346 patent or the '531 application because the '346 or '365 patent or '531 application claims are directed to the same compound as utilized in the presently claimed subject matter, e.g., see claim 5 of the '531 application, page 123 of the application, third compound from the bottom; claims 1-7 of the '346 patent, and claim 5 of the '365 patent, col. 133, lines 10-11.

Also, while the present claims include elements not highlighted in the '365 or '346 patent or the '531 application, claims 16-18, are directed to the same, ultimate objects as in present claim

17 (treating hyperlipidemia) i.e, the mechanisms recited in the claims of '346 patent do not represent a patentably distinct method because ultimately, the claims would be useful for the treatment of hyperlipidemia.

It should be noted that in the above one-way obviousness analysis, the present claims are viewed as being the basis upon which the claims of the '365 of '346 patents or the '531 application could be rejected. Therefore, it is immaterial that the co-pending claims do not include all the method objectives and steps in the present claims. What is ultimately germane is that one could practice the presently claimed subject matter without also practice the subject matter of the '365 or '346 patents or '531 application.

Accordingly, for the above reasons, the claims are deemed properly rejected.

Claims 1-9; 11-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 7-32, 34-52, 54-83 of co-pending Application No. 10/835,916.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the co-pending applications make use of the same compound which is in the present claims, e.g., see claim 1 of the '916 application and therefore in practicing the methods, compositions and/or kits of the co-pending applications, one would necessarily be practicing methods and kits of the present claims.

Additionally, as above, it should be noted that the above one-way obviousness analysis, the claims '916 are viewed as being the basis upon which the claims of the present application could be rejected. Therefore, it is immaterial that the co-pending of the present application could be rejected. Therefore, it is immaterial that the co-pending or present claims do not include all of the method objectives and steps as in the present claims. For example, claim 1 of the '916 application requires the presence of an HMG-CoA reductase inhibitor, while the present claims are silent in this respect. However, the present claims recite comprising, and thus do not patentably exclude an HMG-CoA redeuctase inhibitor from being present. What is ultimately germane is that one could not practice the presently claimed subject matter without also practicing the subject matter of the '916 application.

This is a provisional obviouness-type double patenting rejection because the conflicting claims have not in fact been patented.

Accordingly, for the above reasons, the claims are deemed to be properly objected to/rejected and none are allowed.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anna Pagonakis whose telephone number is 571-270-3505. The examiner can normally be reached on Monday thru Thursday, 9am to 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

10/24/07

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER

AP